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⑪ Publication number:

0 573 975 A1

⑫

## EUROPEAN PATENT APPLICATION

⑬ Application number: 93109233.2

⑮ Int. Cl. 5: C07D 495/04, A61K 31/435,  
//(C07D495/04,333:00,221:00)

⑯ Date of filing: 08.06.93

⑰ Priority: 08.06.92 JP 147189/92  
27.10.92 JP 289041/92

Minami-Ashigara-shi, Kanagawa-ken(JP)

Inventor: Sato, Kozo

c/o FUJI PHOTO FILM CO., LTD.,

No. 210, Nakanuma

Minami-Ashigara-shi, Kanagawa-ken(JP)

Inventor: Suginome, Takashi

c/o FUJI PHOTO FILM CO., LTD.,

2-12-1, Ougi-cho

Odawara-shi, Kanagawa-ken(JP)

⑯ Date of publication of application:  
15.12.93 Bulletin 93/50

⑯ Designated Contracting States:  
CH FR LI

⑰ Representative: Hansen, Bernd, Dr.

Dipl.-Chem. et al

Hoffmann, Eitl & Partner

Patent- und Rechtsanwälte,

Postfach 81 04 20

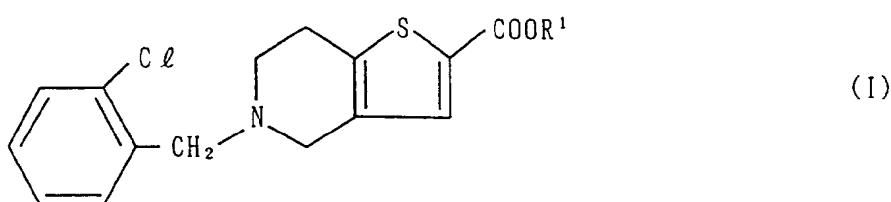
D-81904 München (DE)

⑰ Applicant: FUJI PHOTO FILM CO., LTD.  
No. 210, Nakanuma  
Minami-Ashigara-shi  
Kanagawa-ken(JP)

⑰ Inventor: Yamakawa, Katsuyoshi  
c/o FUJI PHOTO FILM CO., LTD.,  
No. 210, Nakanuma

⑮ 2-alkoxycarbonyl-5-o-chlorobenzyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivative and process for producing the same.

⑯ An intermediate, 2-alkoxycarbonyl-5-o-chlorobenzyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid derivatives of the following general formula (I):



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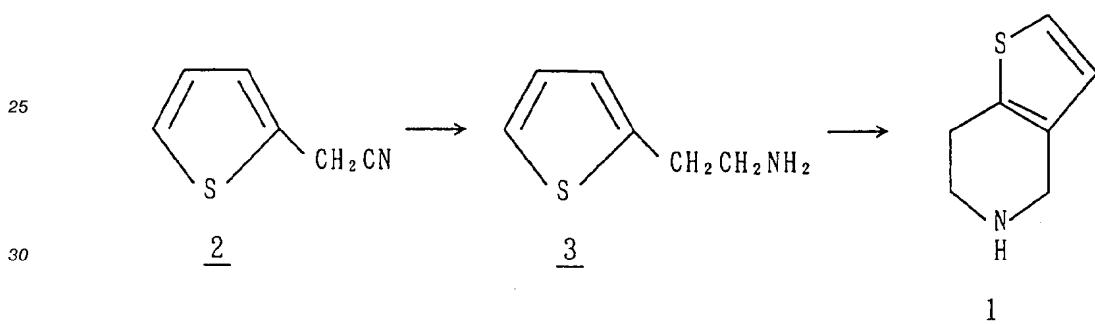
wherein R¹ represents an alkyl group  
and acid salts of them are useful for synthesizing ticlopidine hydrochloride from an inexpensive, easily available compound in short steps.

## Background of the Invention

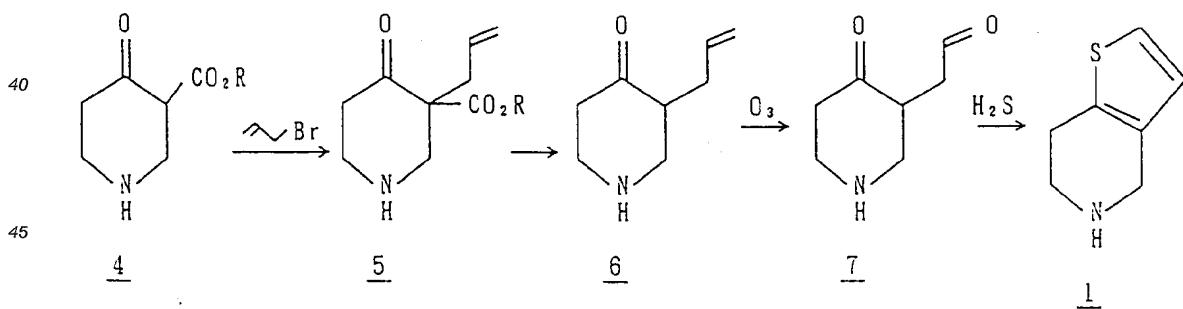
The present invention relates to new synthetic intermediates useful for producing ticlopidine hydrochloride having an effect of inhibiting platelet aggregation in an economical manner on an industrial scale, and a process for producing them.

Reports were made from old times on the synthesis of a 4,5,6,7-tetrahydrothieno[3,2-c]pyridine skeleton of ticlopidine hydrochloride. The processes for the synthesis can be roughly divided into two processes. One is a process wherein a thiophene derivative is used as the starting material and a tetrahydropyridine ring is closed [see, for example, Japanese Patent Publication for Opposition Purpose (hereinafter referred to as "J.P. KOKOHU") No. Sho 56-2068, Japanese Patent Unexamined Published Application (hereinafter referred to as "J.P. KOKAI") No. Sho 62-103088 and EP 439404A2] and the other is a process wherein a piperidone derivative is used as the starting material and a thiophene ring is closed (see, for example, J.P. KOKAI Nos. Sho 63-2992 and Sho 63-126883, EP 360293A2 and DE 2,701,511). Although the former (known reaction scheme 1) comprising only a small number of the reaction steps is an advantageous process, a further improvement is demanded, since it has problems that a cyanide is used as the starting material and that side reactions occur in the course of the reduction. The investigations of the latter (known reaction schemes 2, 3 and 4) were started relatively recently and only a very small number of reports were proposed. Thus no process for producing the intended compound from an inexpensive starting material by short steps has been found yet.

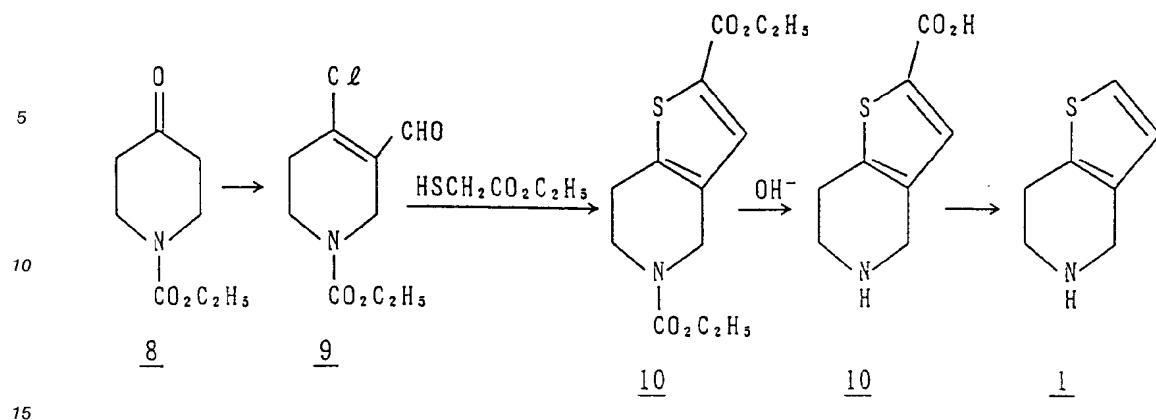
Known reaction scheme 1 (J.P. KOKAI No. Sho 62-103088 etc.)



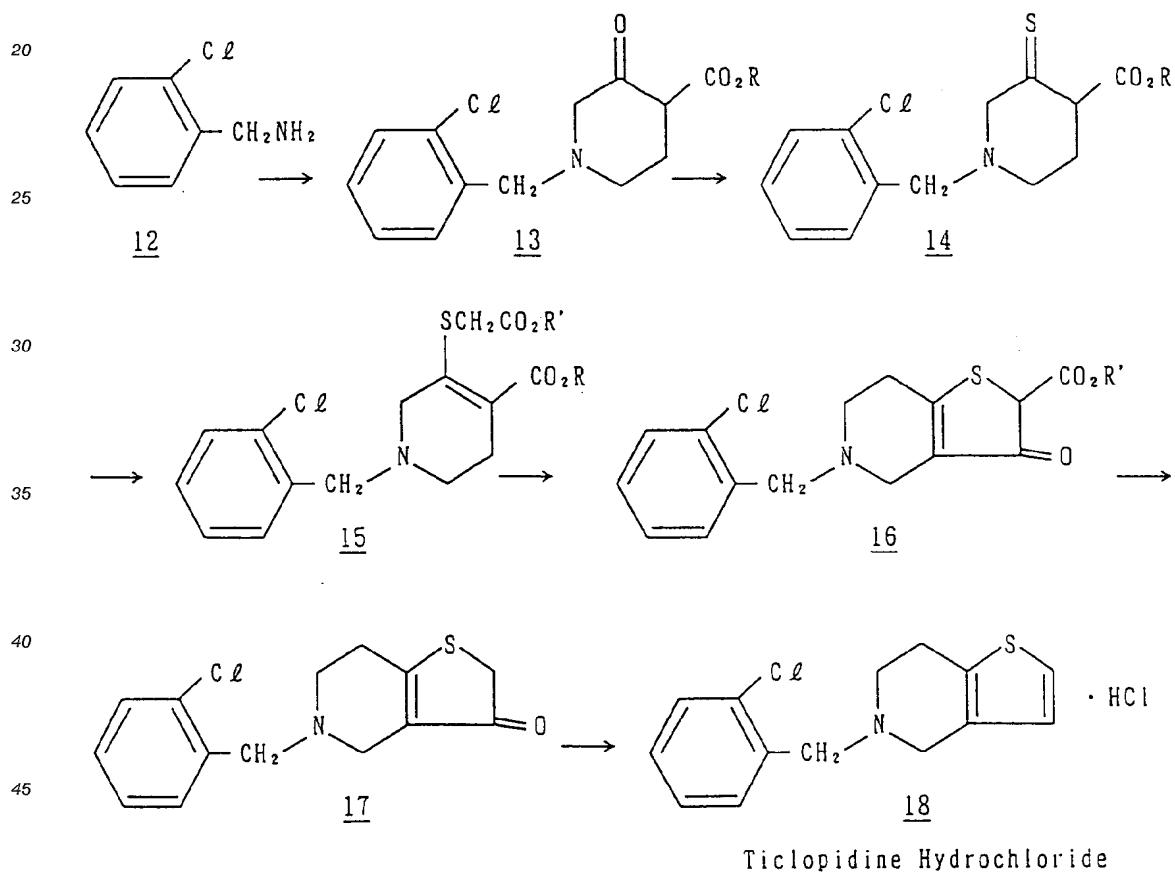
35 Known reaction scheme 2 (EP 360293A2)



50 Known reaction scheme 3 (J.P. KOKAI No. Sho 63-2992)



Known reaction scheme 4 (J.P. KOKAI No. Sho 63-126883)



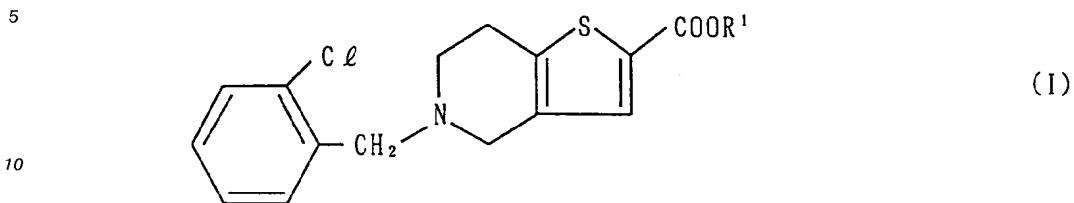
## Summary of the Invention

The object of the present invention is to provide an intermediate useful for synthesizing ticlopidine hydrochloride from an inexpensive, easily available compound in short steps.

55 Another object of the present invention is to provide a process for producing an intermediate useful for synthesizing ticlopidine hydrochloride from an inexpensive, easily available compound in short steps.

These and other objects of the present invention will be apparent from the following description and Examples.

The first aspect of the invention relates to 2-alkoxycarbonyl-5-o-chlorobenzyl-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine-2-carboxylic acid derivatives of the following general formula (I):

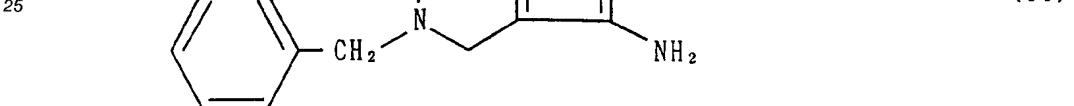


wherein R¹ represents an alkyl group

15 and acid salts of them.

The second aspect of the invention relates to a process for producing a 2-alkoxycarbonyl-5-o-chlorobenzyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivative of the general formula (I), which comprises diazotizing a 2-alkoxycarbonyl-3-amino-5-o-chlorobenzyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivative of the general formula (II):

20



30

wherein R¹ is as defined above.

and then subjecting the thus-obtained diazonium salt to a reductive nitrogen-removing reaction.

#### Detailed explanation of Preferred Embodiments

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The derivatives of the present invention are novel and the derivatives per se are expected to have physiological activities such as anti-thrombogenic activity and the like.

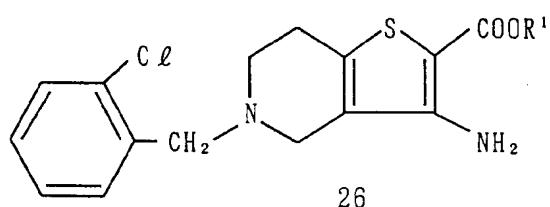
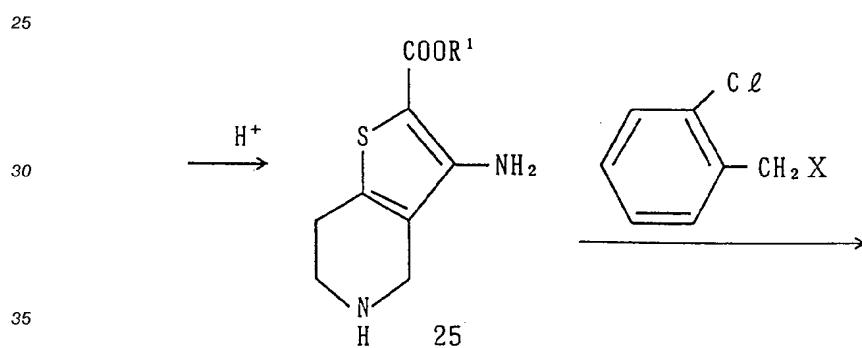
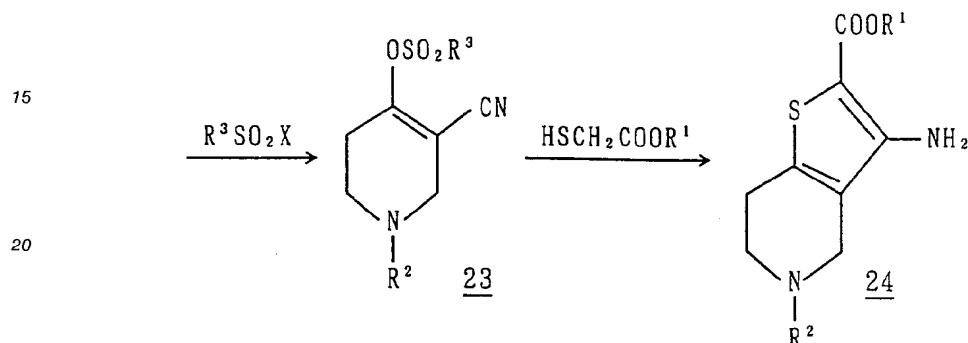
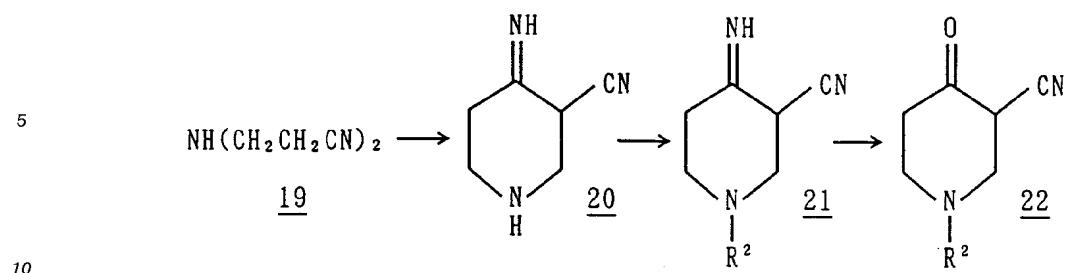
The derivatives of the general formula (I) are synthetic intermediates useful for producing ticlopidine hydrochloride by the following reaction scheme:

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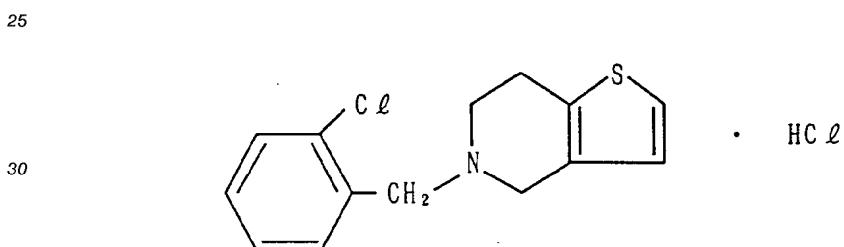
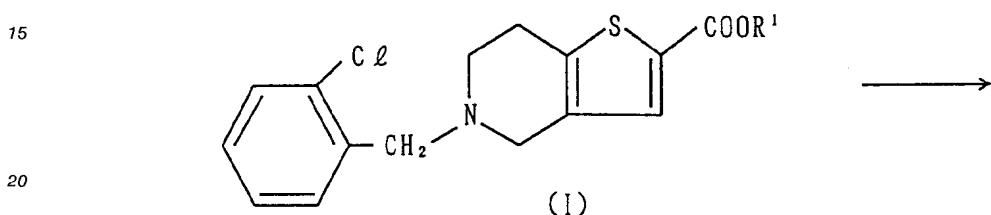
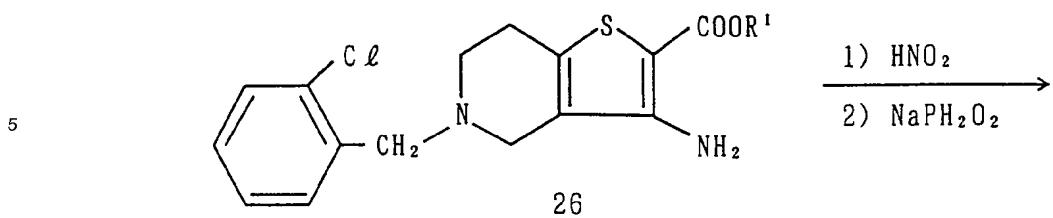
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$\text{R}^3$ : an alkyl or aryl group  
 $\text{X}$ : a halogen



35 Ticlopidine Hydrochloride

The detailed description will be made on the compounds of the present invention hereafter.

40 R¹ in the above general formula (I) represents alkyl groups having preferably 1 to 20 carbon atoms,  
more preferably 1 to 8 carbon atoms (such as methyl, ethyl, butyl and 2-ethylhexyl groups).

The acids capable of forming the acid salt with the compound of the general formula (I) include inorganic acids such as hydrochloric acid, sulfuric acid, hydrobromic acid, etc.; and organic acids such as acetic acid, p-toluenesulfonic acid, etc. The most preferred salt is hydrochloride. The acid salt of the compound of the general formula (I) may be prepared by adding the acid according to the known method.

45 Examples of the compounds of the general formula (I) of the present invention are listed in Table 1.

50

55

Table 1

Compound No.	R <sup>1</sup>
5	(I)-1 CH <sub>3</sub>
	(I)-2 C <sub>2</sub> H <sub>5</sub>
	(I)-3 C <sub>3</sub> H <sub>7</sub>
	(I)-4 C <sub>4</sub> H <sub>9</sub>
	(I)-5 C <sub>8</sub> H <sub>17</sub>
10	(I)-6 C <sub>4</sub> H <sub>9</sub> CH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub>
	(I)-7 C <sub>12</sub> H <sub>25</sub>
	(I)-8 C <sub>14</sub> H <sub>29</sub>
	(I)-9 C <sub>8</sub> H <sub>17</sub> CH(C <sub>6</sub> H <sub>13</sub> )CH <sub>2</sub>
15	(I)-10 C <sub>18</sub> H <sub>37</sub>

The detailed description will be made on the diazotization and reduction reactions to obtain the compound of the general formula (I), referring to the above reaction scheme.

Compound 26 (derivative of the general formula (II)) is synthesized from 3,3'-iminodipropionitrile 19 which is the starting material and easily available on the market at a low cost (Japanese Patent Application No. Hei 4-147185). This compound is deaminated through a diazotization and reduction reactions to obtain a compound of the general formula (I) in a high yield.

R<sup>2</sup> of the compounds 21 to 24 represents an alkylcarbonyl group, arylcarbonyl group, alkylsulfonyl group, arylsulfonyl group, alkoxy carbonyl group or aryloxy carbonyl group and the like, preferably acetyl group. Ticlopidine hydrochloride is produced through a hydrolysis, decarboxylation and the like of the compound of the general formula (I).

The nitrites usable for forming the diazonium compounds include alkali nitrites such as sodium nitrite, potassium nitrite and lithium nitrite. In them, sodium nitrite is particularly preferred. The acids usable for the diazonium-forming reaction are not particularly limited so far as they are capable of liberating nitrous acid from the nitrite. They include, for example, hydrochloric acid, sulfuric acid, hydrobromic acid and acetic acid. In them, hydrochloric acid is particularly preferred. The solvents include water, alcohols, THF, etc. They can be used either singly or in the form of a mixture of them. Particularly preferred solvent is water. The amount of the nitrite used is usually 0.8 to 1.2 mol, preferably 0.9 to 1.1 mol, per mol of the compound of the general formula (II), and the amount of the acid used is 2.0 to 4.0 mol, preferably 2.5 to 3.0 mol, per mol of the nitrite. When excess nitric acid remains in the reaction liquid after completion of the reaction, it can be decomposed by addition of urea. The reaction temperature is usually -5 to 10 °C, preferably 0 to 5 °C.

The reaction time which markedly varies depending on the kinds and relative amounts of the nitrite, acid used and the reaction temperature is usually 0.5 to 5 hours, preferably 1 to 2 hours. After completion of the reaction, the diazonium salt can be isolated. Usually, however, the reaction product is subjected to the subsequent reaction without separation.

Hypophosphorous acid or ethanol is preferably used as the reducing agent for the nitrogen-removing reaction of the diazonium salt obtained as described above since it is inexpensive. Further tributyltin hydride, triethylsilane hydride, sodium borohydride, etc. are also usable. The solvent used for forming the diazonium salt can be used as it is for this reaction. When tributyltin hydride or the like is used, an organic solvent such as diethyl ether, THF or acetonitrile can be used. The amount of the reducing agent is 1 to 100 mol, preferably 1 to 10 mol, per mol of the diazonium salt. The reaction temperature is usually -20 to +20 °C, preferably -10 to +10 °C. The reaction time which markedly varies depending on the variety and amount of the reducing agent used and reaction temperature is usually 0.5 to 3 hours, preferably 0.5 to 2 hours. After completion of the reaction, the intended product can be isolated by an ordinary method such as neutralization, extrusion, extraction, washing, concentration or crystallization. The product can be purified, if necessary, by recrystallization, column chromatography or the like.

Ticlopidine hydrochloride can be easily obtained by subjecting the compound of the general formula (I) to either the hydrolysis and decarboxylation at the same time in the presence of an acid such as hydrobromic acid, or decarboxylation with copper/quinoline after completion of the hydrolysis and isolation of the hydrolyzed compound, or a dealkoxycarboxylation in the presence of lithium iodide-collidine-quinoline) or copper iodide-collidine(quinoline).

The present invention provides a new 2-alkoxycarbonyl-5-o-chlorobenzyl-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine derivative and salt thereof useful for producing ticlopidine hydrochloride having an effect of

inhibiting platelet aggregation in an economical manner on an industrial scale, and an advantageous process for producing them.

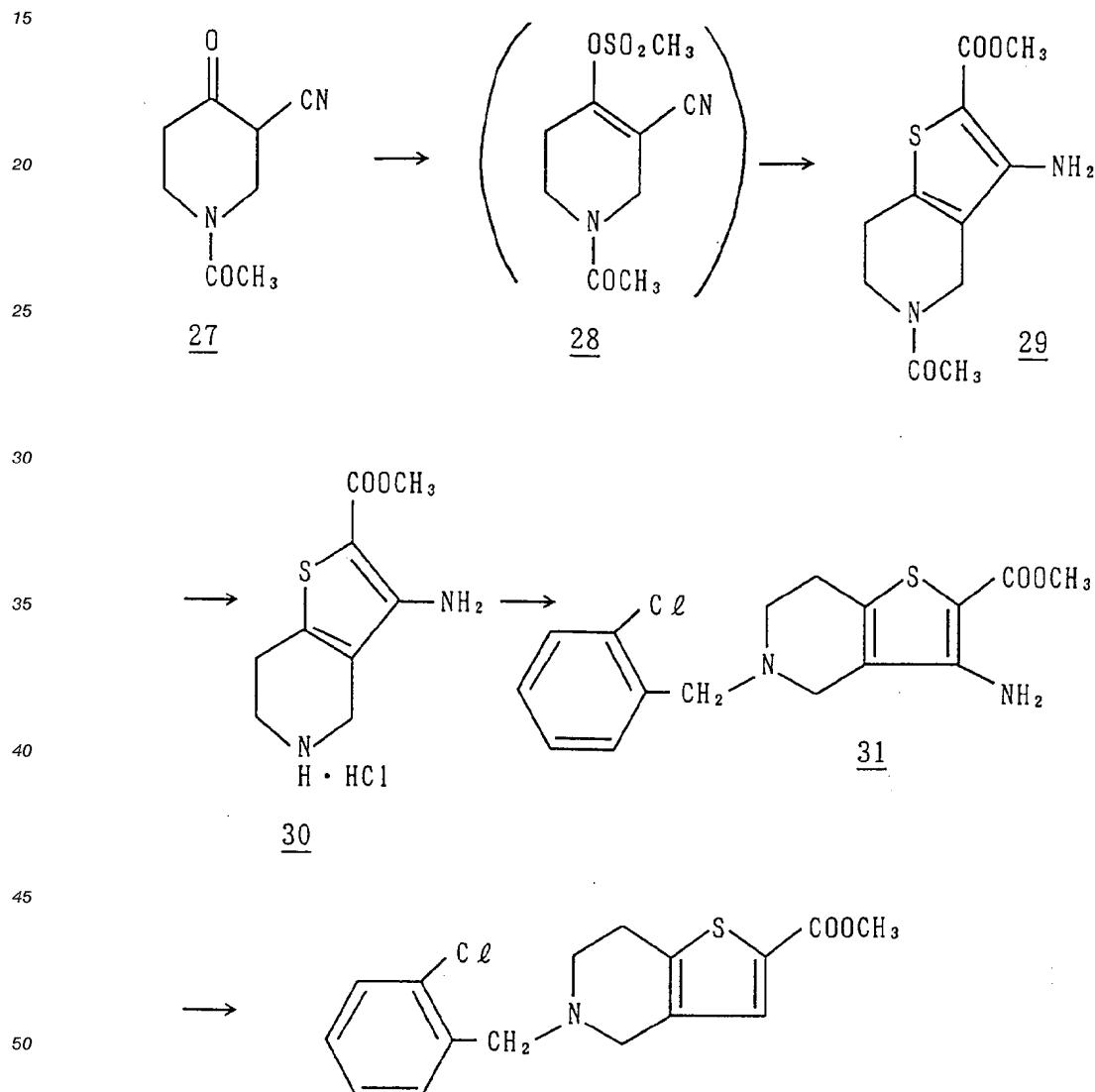
The following Examples are given to illustrate the invention.

5 (Examples)

Examples for syntheses of representative compounds of the present invention and analytical data thereof will be shown below.

10 Example 1 Synthesis of compound (I)-1

Compound (I)-1 was synthesized according to the following reaction scheme:



Compound (I)-1

8.3 g (0.05 mol) of 1-acetyl-3-cyanopiperidine-4-one (27) which is a compound known from a literature was dissolved in 11.9 g (0.15 mol) of pyridine. 5.7 g (0.05 mol) of methanesulfonyl chloride was added

dropwise to the resultant solution under cooling with ice and then the resultant mixture was stirred at room temperature for 30 min. Then 5.4 g (0.05 mol) of methyl thioglycolate was mixed with 19.3 g (0.1 mol CH<sub>3</sub>ONa) of 28 % solution of sodium methylate in methanol. The resultant mixture was stirred for 5 min and then added to the reaction solution obtained as described above. The resultant mixture was stirred at room 5 temperature for 30 min and then cooled with ice. 9.6 g (0.05 mol CH<sub>3</sub>ONa) of 28 % solution of sodium methylate in methanol was added to the reaction solution and the resultant mixture was stirred at room temperature for 30 min.

After completion of the reaction, 800 ml of water was added to the reaction solution. After neutralization (pH 5 to 6) with hydrochloric acid followed by extraction with ethyl acetate (600 ml × 2), the ethyl acetate 10 layer was washed with 500 ml of 3 N aqueous sodium hydroxide solution and then with 500 ml of water. Ethyl acetate was distilled off under reduced pressure and the residue was recrystallised from acetonitrile to obtain 5.8 g (46 %) of methyl 5-acetyl-3-amino-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylate (29).

To 2.54 g of compound 29, 20 ml of methanol and 5.1 ml of concentrated hydrochloric acid were added in this order and then the reaction mixture was heated under reflux for 4 hours. After cooling, the crystals 15 thus precipitated were collected by filtration to obtain 1.70 g of methyl 3-amino-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylate hydrochloride (30). Yield: 68 %.

Melting point: 270 °C or above

<sup>1</sup>H-NMR(200MHz)

δ ppm (DMSO-d<sub>6</sub>): 2.95(2H, t, J = 6.0 Hz), 3.40(2H, t, J = 6.0 Hz), 3.71(3H, s), 3.95(2H, t), 6.60(2H, s), 20 9.76(2H, s).

Subsequently, 2.48 g of compound 30 and 1.61 g of o-chlorobenzyl chloride were dispersed in 20 ml of acetonitrile. 3.1 ml of triethylamine was added to the dispersion and the resultant mixture was heated under reflux for 4 hours. After cooling, ethyl acetate and water were added thereto. After fractionation followed by 25 washing with water, the product was dried over Glauber's salt. The solvent was distilled off and the residue was purified by column chromatography (n-hexane / ethyl acetate = 1/1). The crystals were formed with a solvent mixture of n-hexane / ethyl acetate to obtain 1.42 g (42 %) of methyl 3-amino-5-o-chlorobenzyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylate (31).

Melting point: 120-121 °C

<sup>1</sup>H-NMR(200MHz)

δ ppm (DMSO-d<sub>6</sub>): 2.75(bs, 2H), 3.35(s, 2H), 3.69(s, 3H), 3.77(s, 2H), 6.38(s, 2H), 7.32(m, 4H).

Subsequently, to 3.3 g of compound 31, 3 ml of water and 30 ml of sulfuric acid were added in this order. Then, a solution of 4.2 g of sodium nitrite in 18 ml of water was added dropwise little by little to the reaction mixture at a temperature of 0 to 5 °C under cooling with freezing mixture (ice-methanol) and then the reaction mixture was stirred for 30 minutes. To this, 50 ml of hypophosphorous acid which had been 35 preliminarily cooled with ice was added little by little. After stirring for 1 hour at room temperature, the resultant mixture was poured into 300 ml of water and then neutralized (pH 6) with aqueous solution of sodium hydroxide. The resultant mixture was saturated with salt and then extracted with ethyl acetate (300 ml × 1). The ethyl acetate layer was washed with saturated aqueous solution of salt (200 ml × 2) and then ethyl acetate was distilled off under reduced pressure. The residue was purified by column chromatography (n-hexane / ethyl acetate = 5/1) to obtain 1.6 g (50 %) of compound (I)-1 as an oily substance.

<sup>1</sup>H-NMR(200MHz)

δ ppm (CDCl<sub>3</sub>): 2.87(m, 4H), 3.59(s, 2H), 3.80(m, 2H), 3.85(s, 3H), 7.21(m, 2H), 7.37(m, 1H), 7.43(s, 1H), 7.50(m, 1H).

Other compounds of the present invention can be obtained in the same manner as described above.

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#### Example 2 Compound (I)-4

The following is analytical data of compound (I)-4 synthesized in the same manner as that of Example 1.

50 Colorless crystal

Melting point: 53-55 °C (crystallization solvent: methanol)

<sup>1</sup>H-NMR(200MHz)

δ ppm (CDCl<sub>3</sub>): 0.95(t, 3H, J = 7.0Hz), 1.43(tq, 2H, J = 7.0, 7.0Hz), 1.67(tt, 2H, J = 7.0, 7.0Hz), 2.87(m, 4H), 3.61(s, 2H), 3.80(s, 2H), 4.25(t, 2H, J = 7.0Hz), 7.22(m, 2H), 7.39(dd, 1H, J = 8.7, 3.3Hz), 7.41(s, 1H), 55 7.51(dd, 1H, J = 8.0, 3.0Hz)

Example 3 Compound (I)-6

The following is analytical data of compound (I)-6 synthesized in the same manner as that of Example

1.

5 Oil

 $^1\text{H-NMR}$ (200MHz)

$\delta$  ppm ( $\text{CDCl}_3$ ): 0.85(t, 3H,  $J = 7.0\text{Hz}$ ), 0.87(t, 3H,  $J = 7.0\text{Hz}$ ), 1.28(m, 4H), 1.36(q, 2H,  $J = 7.0\text{Hz}$ ), 1.39(q, 2H,  $J = 7.0\text{Hz}$ ), 1.63(m, 1H), 2.85(m, 4H), 3.60(s, 2H), 3.81(s, 2H), 4.15(d, 2H,  $J = 6.0\text{Hz}$ ), 7.23(m, 2H), 7.36(dd, 1H,  $J = 9.3, 2.7\text{Hz}$ ), 7.38(s, 1H), 7.50(dd, 1H,  $J = 7.2, 2.3\text{Hz}$ )

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Example 4 Compound (I)-9

The following is analytical data of compound (I)-9 synthesized in the same manner as that of Example

1.

15 Oil

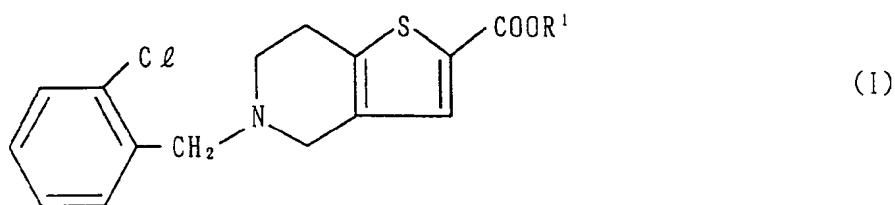
 $^1\text{H-NMR}$ (200MHz)

$\delta$  ppm ( $\text{CDCl}_3$ ): 0.86(t, 6H,  $J = 6.7\text{Hz}$ ), 1.24(m, 24H), 1.71(m, 1H), 2.88(m, 4H), 3.60(s, 2H), 3.79(s, 2H), 4.14(d, 2H,  $J = 6.0\text{Hz}$ ), 7.23(m, 2H), 7.36(dd, 1H,  $J = 8.6, 2.0\text{Hz}$ ), 7.39(s, 1H), 7.50(dd, 1H,  $J = 6.7, 2.0\text{Hz}$ )

20 **Claims**

1. A compound of the general formula (I):

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wherein  $R^1$  represents an alkyl group

35 and acid salts thereof.

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2. The compound and acid salt thereof according to claim 1 wherein  $R^1$  is an alkyl group having 1 to 20 carbon atoms.

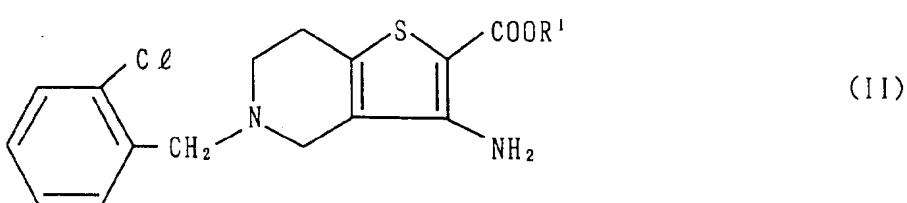
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3. The compound according to claim 2 wherein  $R^1$  is an alkyl group having 1 to 8 carbon atoms.

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4. A process for producing a compound of the general formula (I) as defined in claim 1, which comprises diazotizing a compound of the general formula (II):

55



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wherein  $R^1$  represents an alkyl group

65 and then subjecting the thus-obtained diazonium salt to a reductive nitrogen-removing reaction.

5. The process according to claim 4 wherein  $R^1$  is an alkyl group having 1 to 20 carbon atoms.

6. The process according to claim 5 wherein R<sup>1</sup> is an alkyl group having 1 to 8 carbon atoms.
7. The process according to claim 4 wherein the amount of the nitrite is 0.8 to 1.2 mol per mol of the compound of the general formula (II).
- 5 8. The process according to claim 4 wherein the acid used for the diazonium-forming reaction is hydrochloric acid, sulfuric acid, hydrobromic acid or acetic acid and the amount of the acid is 2.0 to 4.0 mol per mol of the nitrite.
- 10 9. The process according to claim 4 wherein the reductive nitrogen-removing reaction is carried out using hypophosphorous acid or ethanol as a reducing agent.
10. The process according to claim 6 wherein the amount of the nitrite is 0.8 to 1.2 mol per mol of the compound of the general formula (II), the acid used for the diazonium-forming reaction is hydrochloric acid, sulfuric acid, hydrobromic acid or acetic acid, the amount of the acid is 2.0 to 4.0 mol per mol of the nitrite, and the reductive nitrogen-removing reaction is carried out using hypophosphorous acid or ethanol as a reducing agent.
- 20 11. Use of a compound of the general formula (I) as defined in claim 1 for a pharmaceutical composition for treatment of thrombogenesis.

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EUROPEAN SEARCH REPORT

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PAGE1

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, PART II no. 1-2, 1978, pages II-48 - II-54 J.-P. MAFFRAND ET AL. 'Nouvelles synthèses de thiéno[3,2-c]pyridines' * page II-48, compounds 1 and 2 * ---	1,3	C07D495/04 A61K31/435 //(C07D495/04, 333:00,221:00)
A	FR-A-2 447 923 (AUSONIA FARMACEUTICI SRL) * page 1, line 1 - line 13 * ---	1,11	
A	FR-A-2 571 055 (NISSHIN FLOUR MILLING CO. LTD.) * page 1, line 1 - line 25 * ---	1,11	
A	PATENT ABSTRACTS OF JAPAN vol. 12, no. 373 (C-534)(3220) 6 October 1988	1,11	
D	& JP-A-63 126 883 (ZOKI SEIKAGAKU KENKYUSHO K.K.) 30 May 1988 ---		
A	CHEMICAL ABSTRACTS, vol. 109, no. 13, 26 September 1988, Columbus, Ohio, US; abstract no. 110409s, page 622 ;	1,11	
D	& JP-A-63 002 992 (DAITO KOEKI CO., LTD.) 7 January 1988 ---		
A	CHEMICAL ABSTRACTS, vol. 83, no. 23, 8 December 1975, Columbus, Ohio, US; abstract no. 193276q, page 464 ; & JP-A-75 011 397 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 30 April 1975 ---	3	
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
BERLIN	16 SEPTEMBER 1993	HASS C.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone	Y : particularly relevant if combined with another document of the same category		
A : technological background	O : non-written disclosure		
P : intermediate document			



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## EUROPEAN SEARCH REPORT

Application Number

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PAGE2

DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	<p>CHEMICAL ABSTRACTS, vol. 79, no. 11, 17 September 1973, Columbus, Ohio, US; abstract no. 66340y, page 449 ; &amp; JP-A-73 015 957 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 18 May 1973</p> <p>-----</p>	3
<b>CLASSIFICATION OF THE APPLICATION (Int. Cl.5)</b>		
<b>TECHNICAL FIELDS SEARCHED (Int. Cl.5)</b>		
<b>The present search report has been drawn up for all claims</b>		
Place of search	Date of completion of the search	Examiner
BERLIN	16 SEPTEMBER 1993	HASS C.
CATEGORY OF CITED DOCUMENTS		
X : particularly relevant if taken alone		T : theory or principle underlying the invention
Y : particularly relevant if combined with another document of the same category		E : earlier patent document, but published on, or after the filing date
A : technological background		D : document cited in the application
O : non-written disclosure		L : document cited for other reasons
P : intermediate document		& : member of the same patent family, corresponding document